Orthopaedic Surgery

CLINICAL ARTICLE OPEN ACCESS

Selecting the Substantially Touched Vertebra as the Lowest Instrumented Vertebra in Spinal Surgeries for *B3GALT6*-Related Disorders: Clinical Experience and Literature Review

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Received: 23 October 2024 | **Revised:** 12 March 2025 | **Accepted:** 27 April 2025

Funding: This research was funded in part by the National Key Research and Development Program of China (2023YFC2507700 to T.J.Z. and N.W., 2022YFC2703102 to N.W., 2022YFC2703901 to Z.W.), National Natural Science Foundation of China (82172525 to G.Q.), National High Level Hospital Clinical Research Funding (2022-PUMCH-D-004 to N.W. and T.J.Z., 2022-PUMCH-C-033 to N.W. and 2022-PUMCH-D-002 to Z.W.), CAMS -Innovation Fund for Medical Sciences (2021-12 M-1-051 to T.J.Z. and N.W., 2021-12 M-1-052 to Z.W., 2022-I2M-2-001 to Z.W., and 2023-I2M-C&T-A-003 to T.J.Z.).

Keywords: Ehlers-Danlos syndrome | genetic testing | joint instability | operative | scoliosis | surgical procedures

ABSTRACT

Objectives: *B3GALT6*-related disorders are characterized by severe early-onset spinal deformities requiring surgical corrections but are associated with increased risks of perioperative complications. This study reports the clinical experience and outcomes of selecting the substantially touched vertebra (STV) as the lowest instrumented vertebra (LIV) in spinal surgeries for patients with *B3GALT6*-related disorders, a group of extremely rare skeletal and connective tissue disorders.

Methods: This retrospective study included patients who were molecularly diagnosed with *B3GALT6*-related disorders and received spinal surgeries for (kypho)scoliosis between 2017 and June 2023. Their medical records were reviewed. We also conducted a systematic literature review to identify (kypho)scoliosis management in patients with *B3GALT6*-related disorders.

Results: We identified a total of four patients. Patient 1 presented with severe kyphoscoliosis and segmentation defects and received a pedicle subtraction osteotomy with short fusion and dual growing rods from T3 to L3. However, coronal imbalance was observed at the 18-month follow-up. Genetic testing revealed biallelic disease-causing variants in *B3GALT6*. A revision surgery was successfully performed, with the level of the LIV extended to the STV (L4). The LIV was similarly extended to the STV in the index surgery for subsequent Patients 2 and 3 who received preoperative genetic testing results, and no complication has

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been observed. Patient 4 underwent preoperative Halo-pelvic traction to minimize complications, followed by posterior spinal fusion. The curves were successfully reduced without complications. A systematic literature review identified 86 articles reporting (kypho) scoliosis management in 12 of the 63 patients with *B3GALT6*-related disorders. Limited surgical experience has been reported, with an increased rate of complications, including death.

Conclusions: Selecting the STV as the LIV is recommended in spinal surgeries for patients with *B3GALT6*-related disorders, considering the characteristic joint hypermobility associated with the condition. Additionally, preoperative Halo-pelvic traction may also be safe and effective. Furthermore, preoperative molecular diagnosis is essential for enabling precision medicine and minimizing complications.

1 | Introduction

Early-onset scoliosis (EOS) is defined as a spinal curvature ≥ 10° occurring before 10 years old and is etiologically classified into congenital or structural, neuromuscular, syndromic, and idiopathic [1, 2]. Syndromic scoliosis refers to the curves associated with systemic disorders, typically rare genetic conditions such as Ehlers-Danlos syndromes (EDS), Down syndrome, and Prader-Willi syndrome [3]. Surgeries in patients with syndromic scoliosis are often associated with a significantly higher rate of perioperative complications, which vary depending on the specific features of the underlying diseases [4].

B3GALT6 (HGNC: 17978) is an evolutionarily conserved single exon gene mapped to 1p36.33. *B3GALT6* encodes a beta-1,3-galactosyltransferase, an enzyme that resides in the medial Golgi apparatus and is important for the extracellular matrix (ECM) [5]. This enzyme transfers a galactose unit during the formation of a tetrasaccharide linkage region, which attaches one or more glycosaminoglycan (GAG) chains to a core protein, thereby initiating the biosynthesis of a proteoglycan (PG) [5]. PGs are present within the ECM and play a crucial role in the regulation of the function of connective tissues as well as cell–cell interactions, cell proliferation, and migration, and other processes [6–8]. Pathogenic variants in *B3GALT6* disrupt the biosynthesis of PGs, leading to skeletal dysplasia phenotypes.

Traditionally, *B3GALT6* is associated with three distinct diseases: Al-Gazali syndrome (ALGAZ, OMIM 609465), Ehlers-Danlos syndrome, spondylodysplastic type 2 (spEDS-B3GALT6, OMIM 615349), and Spondyloepimetaphyseal dysplasia with joint laxity, type 1, with or without fractures (SMED-JL1, OMIM 271640). ALGAZ is characterized by pre- and post-natal growth retardation, joint contractures with camptodactyly, radio-ulnar synostosis, bilateral talipes equinovarus, generalized osteoporosis, anterior segment eye anomalies, and early lethality [9, 10]. spEDS-*B3GALT6* is one of the 15 subtypes of EDS, characterized by progressive short stature, muscle hypotonia, and bowing of limbs [11, 12]. Specific features commonly seen in Orthopedics include congenital or early onset, progressive kyphoscoliosis, generalized hypermobility or hypermobility limited to the distal joint [13]. Frequently reported radiographic features are platyspondyly, anterior beak of the vertebral body, short ilium, generalized osteoporosis, and so forth [13]. Patients with SMED-JL1 usually present with vertebral abnormalities and ligamentous laxity, elbow deformities, hip dislocations, and talipes equinovarus [14]. The increasingly recognized phenotypic overlap suggests that the three conditions may not be separate clinical entities and are therefore grouped into "*B3GALT6*-related disorders" under "linkeropathies" [6, 15, 16].

B3GALT6-related disorders are extremely rare, with only a limited number of cases reported in the literature, and the exact prevalence and incidence remain unknown. The above-mentioned connective tissue defects and skeletal dysplasia affect multiple systems of the body, significantly overlapping with other linkeropathies, HCTDs, and skeletal dysplasias, which results in considerable challenges in both diagnosis and treatment. Spinal deformity is one of the clinical hallmarks of *B3GALT6*-related disorders, such as congenital or early-onset and progressive kyphoscoliosis, platyspondyly, and anterior beak of vertebral body [6, 13, 17]. It is well recognized that severe curvature of the spine can impair respiratory and cardiac functions, and thus early and effective interventions are lifesaving.

Spinal surgeries in patients with *B3GALT6*-related disorders are challenging due to their multisystemic nature and tissue fragility. Vascular fragility is recognized as part of the phenotypes [18]. Joint hypermobility, muscle hypotonia, osteoporosis, and lung hypoplasia are frequently observed as well [13]. These common features contribute to the complexities of the surgical procedure, while relevant experience in this field is limited. Although growing rod implantation and spinal fusion have been utilized in patients with *B3GALT6*-related spinal deformity, detailed information is unavailable [19–21]. Additionally, repeat surgical procedures and postoperative death have been observed in this group of patients [21, 22]. Therefore, the development of effective and safe surgical strategies is crucial for the improvement of postoperative clinical outcomes.

The purpose of this study was to summarize our experience and provide management options for patients with *B3GALT6*-related disorders to reduce complications and improve clinical outcomes. Specifically, we focused on (i) detailed operative plans and clinical outcomes for selecting the lowest instrumented vertebra (LIV), considering hypermobile joints, as well as the feasibility of using Halo-pelvic traction; (ii) a review of management strategies reported in previous studies; and (iii) the utility of molecular diagnosis in guiding personalized treatment planning.

2 | Methods

2.1 | Patient Recruitment

Patients who were molecularly diagnosed with *B3GALT6*-related disorders and received spinal surgeries at Peking Union Medical College Hospital (PUMCH) and Peking University First Hospital between 2017 and June 2023 were recruited under the framework of the Deciphering disorders Involving Scoliosis and COmorbidities (DISCO) study (https://discostudy.org/). A

retrospective review of medical records was conducted, including preoperative demographics, genetic test results, surgical records, and radiographs.

2.2 | Molecular Diagnosis

Genetic testing was carried out using blood samples. Methods of genetic testing included trio or proband-only exome sequencing (ES) or genome sequencing (GS). The raw data were processed as previously reported using our in-house developed Peking Union Medical College Hospital Pipeline (PUMP) [23–25]. The data was analyzed in accordance with ACMG/AMP Guidelines [26, 27]. Patients harboring biallelic disease-causing variants in *B3GALT6* were molecularly diagnosed with *B3GALT6*-related disorders. Disease-causing variants were defined as being classified as pathogenic or likely pathogenic variants according to ACMG/AMP Guidelines, or variants of uncertain significance when no other variants detected by GS or ES were interpreted as more probable contributors to the observed phenotypes.

2.3 | Surgical Strategy

The surgical approach was determined by experienced surgical teams based on the patient's clinical presentation, including the severity and rigidity of the spinal deformity, neurological involvement, evidence of bone dysplasia, age, skeletal maturity, and growth potential. These factors were assessed through physical examination and imaging techniques, including whole spine x-rays, side-bending x-rays, computed tomography (CT) scans, and magnetic resonance imaging (MRI). When available, the molecular diagnosis obtained prior to surgery was also considered. Patients with severe, rigid scoliosis received preoperative short-term halo-pelvic traction when necessary [28]. The surgical procedure of the corrective surgery has been detailed in our previous studies [29–31]. In brief, the patient was positioned prone on a radiolucent table under general anesthesia. Incisions were made, and the appropriate spinal levels were exposed subperiosteally. Short segmental fusion, dual growing rod implantation, or posterior vertebral column resection was then performed. Intraoperative neurophysiologic monitoring of the spinal cord, including somatosensory evoked potentials, motor evoked potentials, and electromyography, was employed during all surgical procedures. For patients suspected of having hereditary connective tissue disorders (HCTDs), tissues were manipulated gently to minimize damage and blood loss, and special caution was paid to positioning to avoid joint dislocations, following the Guidelines on the diagnosis and treatment of EDS [32]. Postoperative bracing was applied for a minimum of 3 months.

2.4 | Evaluation of Radiographs

Preoperative, postoperative, and follow-up x-rays were retrieved for analysis. Parameters were measured using AlignProCARE, including 3-dimensional deformity parameters, the main curve degree, upper thoracic kyphosis (UTK), thoracic kyphosis, thoracolumbar junction curve, and lumbar lordosis [33]. T1–T12 height, T1–S1 height, and Campbell's space available for lung (SAL) ratio were obtained to evaluate spinal and chest growth.

2.5 | Literature Review

We performed a literature review in PubMed to identify (kypho)scoliosis management strategies in patients with *B3GALT6*-related disorders. The searching string was "(((B3GALT6) OR (Al-Gazali syndrome)) OR (spondylodysplastic Ehlers-Danlos syndrome)) OR (Spondyloepimetaphyseal dysplasia with joint laxity)." Primary articles reporting patients with molecularly confirmed *B3GALT6*-related disorders were included. Molecular confirmation was defined as the identification of biallelic variants considered disease-causing by the authors. If spinal manifestations or management were not explicitly mentioned, the corresponding information was recorded as "N/A (not available)."

2.6 | Ethics Statement

This study was approved by the Ethics Committee at Peking Union Medical College Hospital (I-22PJ976) and the Ethics Committee at Peking University First Hospital (2021-285). Written informed consent was obtained from each patient's legal guardian.

3 | Results

3.1 | Clinical Experience

We report our surgical experience in four patients molecularly diagnosed with *B3GALT6*-related disorders. Demographic data, radiographic measurements, and the growth of the spine and chest are shown in Table 1. The first patient experienced postoperative L3-L4 facet dislocation, resulting in an adding-on phenomenon. After a molecular diagnosis of *B3GALT6*-related disorders, he received revision surgery with an instrumentation stop at the STV. Outcomes after the 7th growing rod extension were satisfactory. The subsequent two patients received their molecular diagnoses before surgeries, and the STV was selected as the LIV during the index surgery. The fourth patient received posterior spinal fusion with bone grafting following Halo-pelvic traction. No fusion level-associated postoperative complications have been observed in the latter three patients.

3.2 | Patient 1

Patient 1, a 4-year-old male, presented with severe kyphoscoliosis and segmentation defects, was admitted for surgical correction, following the failure of a 1-year bracing treatment. X-rays revealed a right thoracic curve of 60°, a thoracolumbar curve of 88°, and a T5 to T12 thoracic kyphosis of 65° (Figure 1A–D). He received posterior pedicle subtraction osteotomy (T12), and a dual growing rod instrumentation applied from T3 to L3. Immediately after surgery, the thoracic curve was 5°, the thoracolumbar curve was 5°, and the kyphotic curvature was 11°, indicating a satisfactory result (Figure 1E,F, Table 1). However, at the

TABLE 1 | Patient demographics, molecular diagnosis, and radiograph measurements.

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Male	Male	Female
Age at surgery, yrs	4	4	6	14
Instrumented levels during the first surgery	T3-L3	T2-L4	T4-T10	T1-L3
Treatment (follow-up) duration, yrs	5.15	2.16	0.25	0.5
Variant 1, classification and origin	NM_080605.4(*B3GALT6*): c.513_520del (p.Glu174Alafs*266), P, paternal	NM_080605.4(*B3GALT6*): c.694C>T(p.Arg232Cys), LP, paternal	NM_080605.4(*B3GALT6*): c.582_583insT(p. Gly195Trpfs*248), LP, paternal	NM_080605.4(*B3GALT6*): c.694C>T(p. Arg232Cys), LP, N/A
Variant 2, classification and origin	NM_080605.4(*B3GALT6*): c.694C>T(p.Arg232Cys), LP, maternal	NM_080605.4(*B3GALT6*): c.180delA(p.Val61Cysfs*15), LP, maternal	NM_080605.4(*B3GALT6*): c.505G>A(p.Glu169Lys), VUS, maternal	NM_080605.4(*B3GALT6*): c.733_734del(p. Leu245Glyfs*197), LP, N/A
Radiographic Characteristic				
Thoracolumbar curve (°)				
Pre	88	32	80	95
Post	5	7	18	58
FU	15	4	30	56
Thoracic curve (°)				
Pre	60	50	34	89
Post	5	15	14	62
FU	17	8	27	58
Lumbar lordosis (°)				
T10-L2				
Pre	38	1	−13	15.6
Post	2	2	−5	10.5
FU	2	1	0.5	10.26
T12-S1				
Pre	−56	−51	−61	−87.2
Post	−41	−53	−56	−56.9
FU	−47	−54	−65	−76.23
Thoracic kyphosis (°)				
T2-T5				
Pre	9	7	8	29
Post	7	10	5	18
FU	7	13	2	5
T5-T12				
Pre	65	12	80	101

(Continues)

TABLE 1 | (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4
Post	11	10	54	9
FU	17	10	58	8
T1-S1 height (cm)				
Pre	19	25	25	23
Post	24	26	31	43
FU	36	28	30	41
T1-T12 height (cm)				
Pre	9	14	15	13
Post	14	15	18	23
FU	16	16	18	23
Length of instrumentation (cm)				
Post	19	24	17	29
FU	29	26	17	35
SAL ratio (%)				
Pre	81	88	61	57
Post	93	91	90	92
FU	98	92	99	90

Abbreviations: FU, latest follow-up; Post, immediate postoperative; Pre, preoperative; SAL, Campbell's space available for lung.

18-month follow-up, coronal imbalance was observed, leading to distal adding-on. The thoracic curve progressed to 35°, and the thoracolumbar curve progressed to 44° (Figure 1G,H, Table S1).

The patient was suspected of having a genetic disorder due to the rarity of the postoperative complication and multisystemic abnormalities revealed by deep phenotyping, including short stature, slightly limited elbow extension, finger joint hypermobility, mitral insufficiency, mitral valve prolapse, and renal cysts. A trio-ES was conducted, and the result has been reported in our previous study [25]. The analysis identified a pathogenic variant NM_080605.4(*B3GALT6*):c.513_520del(p.Glu174Alafs*266) inherited from the father and a likely pathogenic variant NM_080605.4(*B3GALT6*):c.694C>T(p.Arg232Cys) inherited from the mother. The patient was therefore diagnosed with *B3GALT6*-related disorders. Joint hypermobility is one of the hallmarks of *B3GALT6*-related disorders and might lead to the adding-on phenomenon at the junction of the instrumented and non-instrumented segments. Therefore, revision surgery with growing rod distraction was performed, during which the LIV was extended to the STV (L4). Early postoperative and follow-up outcomes after the 7th growing rod extension were satisfactory (Figure 1I–L). The length of the spine increased by 13 cm at T1-T12 and 17 cm at T1-S1, and the SAL ratio also improved (Table 1).

3.3 | Patient 2

Patient 2 had his initial visit at the age of 4 due to kyphoscoliosis, which did not respond to 1 year of bracing treatment. X-rays showed a thoracic curve of 50° and a thoracolumbar curve of 32°, along with evidence of platyspondyly (Figure 2A,D, Table 1). Preoperative examinations indicated multisystemic involvement including short stature, pectus deformity, limited elbow movement, pes planus, and left atrial enlargement. He also had a history of hydrocephalus and presented with increased head circumference. Due to suspicion of a genetic disorder, a trio-GS was ordered. The test revealed a likely pathogenic variant NM_080605.4(*B3GALT6*):c.694C>T(p.Arg232Cys) inherited from the father and a likely pathogenic variant NM_080605.4(*B3GALT6*):c.180delA(p.Val61Cysfs*15) inherited from the mother. Patient 2 was diagnosed with *B3GALT6*-related disorders. Based on earlier experiences treating Patient 1, the STV (T4) was selected as the LIV. Patient 2 received posterior scoliosis correction and dual growing rods instrumentation from T2 to T4. Postoperative Cobb angles of the thoracic and thoracolumbar curves were 15° and 7° (Table 1). Early postoperative and follow-up outcomes after 3rd growing rod extension were satisfactory (Figure 2E,H). No fusion level-associated complication was observed after the initial surgery or three subsequent growing rod distractions. At the latest follow-up, the length of the spine increased by 7 cm at T1-T12 and 17 cm at T1-S1, and the SAL ratio also improved (Table 1).

3.4 | Patient 3

Patient 3 was a 6-year-old male. He was diagnosed with scoliosis at 7 months old. His scoliosis worsened after a 6-month course of growth hormone therapy and was surgically corrected at 4 years old. Upon his initial visit to our clinic, his chief complaint was progression of the curve after another course of growth hormone therapy. X-rays demonstrated a thoracic curve of 34°, a

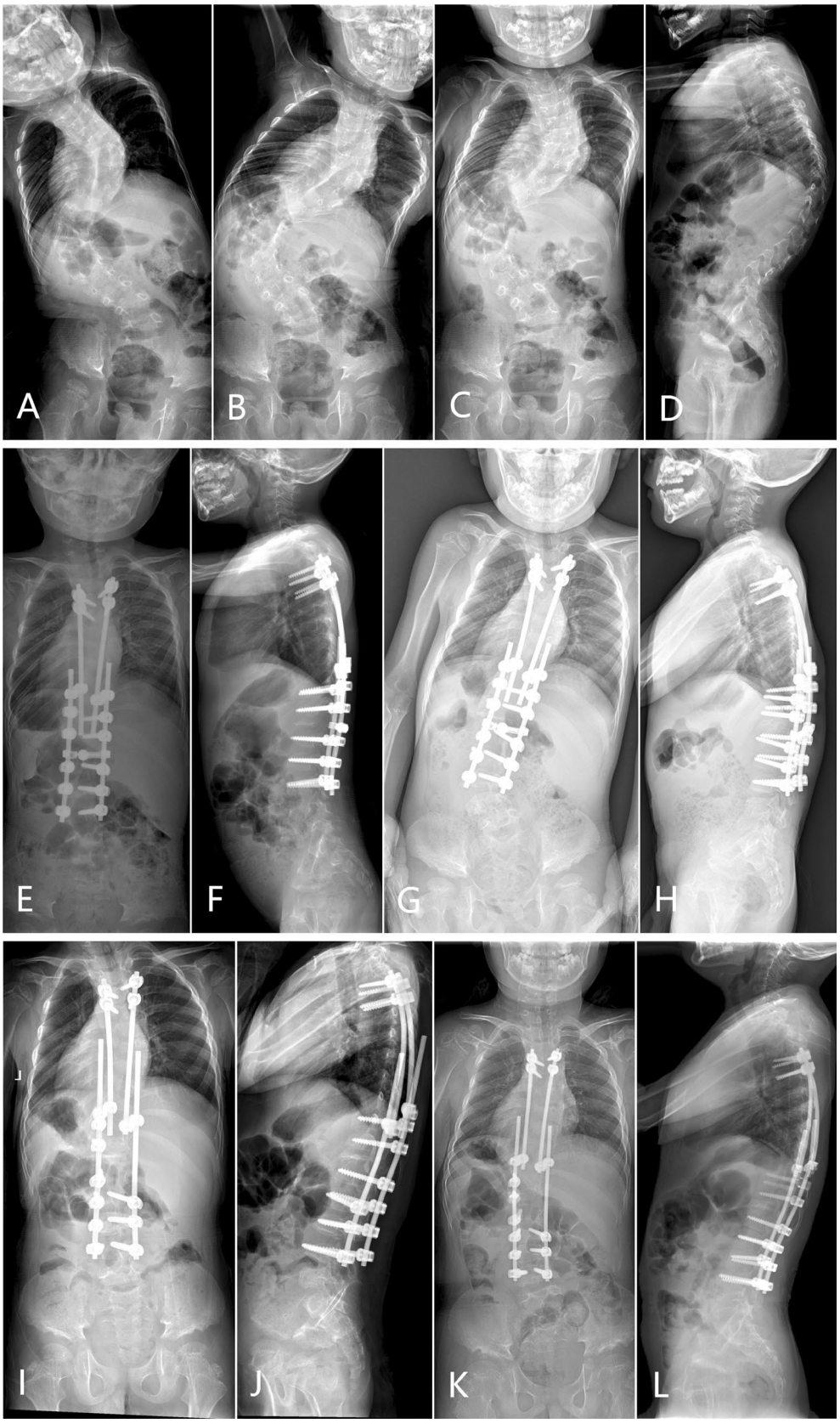

FIGURE 1 | X-rays of Patient 1. (A–D): Preoperative X-rays at the age of 4, including side-bending X-rays (A, B) and whole spine X-rays (C, D). (E, F) Immediate postoperative x-rays after the initial surgery. (G, H) X-rays at 18 months after the initial surgery indicating a coronal imbalance. (I, J) Immediate postoperative X-rays after the revision surgery, during which the level of the lowest instrumented vertebra was extended from L3 to L4. (K, L) X-rays at the latest follow-up after the 7th growing rod extension.

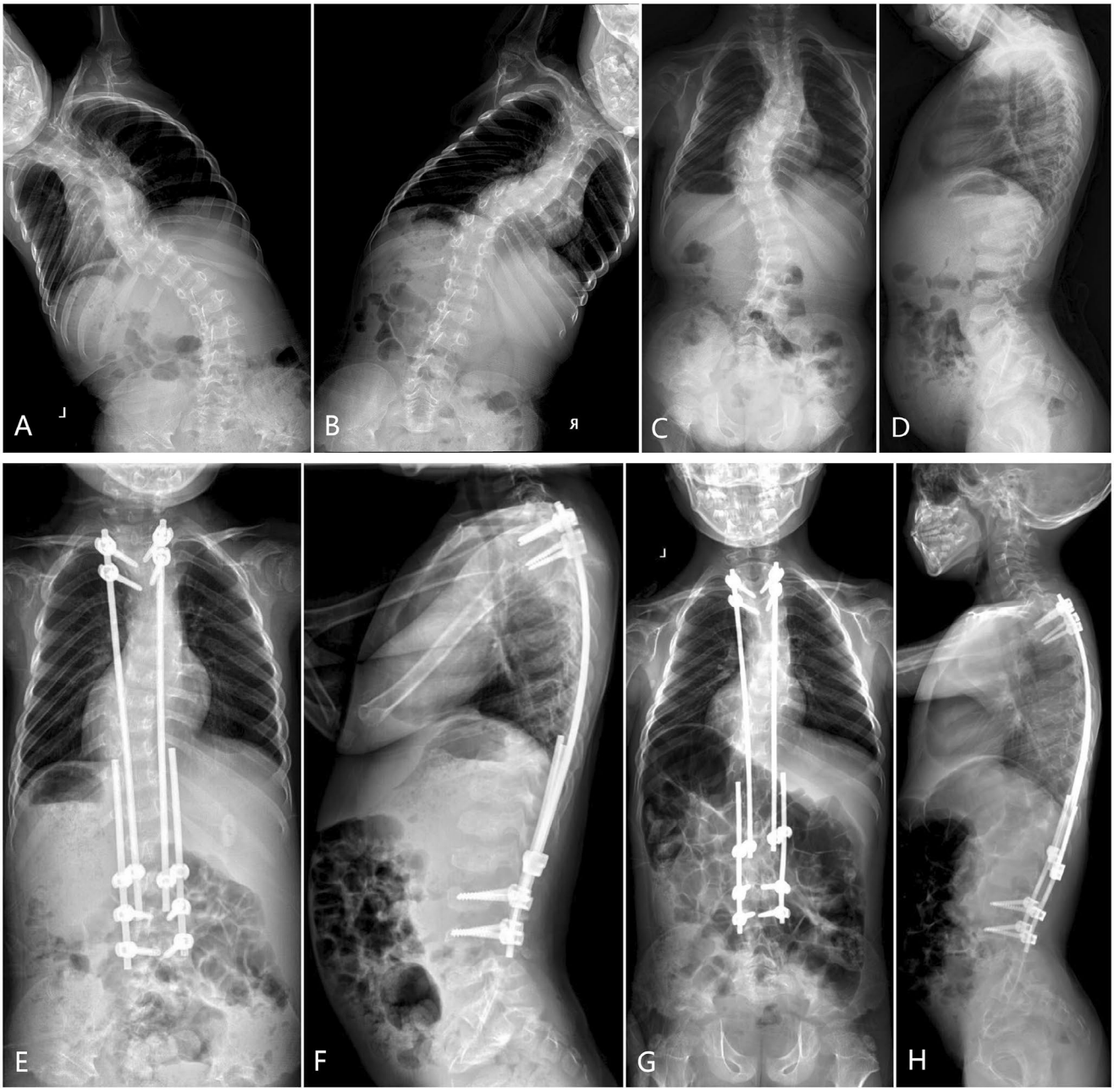

FIGURE 2 | X-rays of Patient 2. (A, D): Preoperative x-rays at the age of 4, including side-bending X-rays (A, B) and whole spine X-rays (C, D), showing a thoracic curve of 50°, a thoracolumbar curve of 32°. (E, F) Immediate postoperative x-rays after the initial surgery. (G, H) X-rays at the latest follow-up after the 3rd growing rod extension.

thoracolumbar curve of 80°, and a T5–T12 thoracic kyphosis of 80° (Table 1). He also exhibited short stature and aortic tortuosity, all of which suggested the presence of an underlying syndromic condition. A trio-GS identified a likely pathogenic variant NM_080605.4(*B3GALT6*):c.582_583insT(p.Gly195Trpfs*248) inherited from the father and a variant of uncertain significance NM_080605.4(*B3GALT6*):c.505G>A(p.Glu169Lys) from the mother. He underwent a T8 vertebral column resection, kyphoscoliosis correction, and internal fixation from T4 to T10. The immediate postoperative course was uneventful. X-rays at the 3-month follow-up showed a thoracic curve of 30° and a thoracolumbar curve of 27°, and the kyphosis was 58° (Table 1). Unfortunately, Patient 3 was lost to follow-up after this point.

3.5 | Patient 4

Patient 4, a 14-year-old female, presented with kyphoscoliosis and respiratory insufficiency. X-rays showed a thoracic curve of 89°, a thoracolumbar curve of 95°, and a T5–T12 thoracic curve of 101° (Figure 3A,E, Table 1). She also presented with short stature, elbow deformity, and hyperextensibility of the knees. A singleton-GS revealed a likely pathogenic variant NM_080605.4(*B3GALT6*):c.694C>T(p.Arg232Cys) and a likely pathogenic variant NM_080605.4(*B3GALT6*):c.733_734delCT(p.Leu245Glyfs*197). The patient underwent preoperative Halo-pelvic traction to minimize complications. Three months later, the thoracic curve was reduced to 71°, the

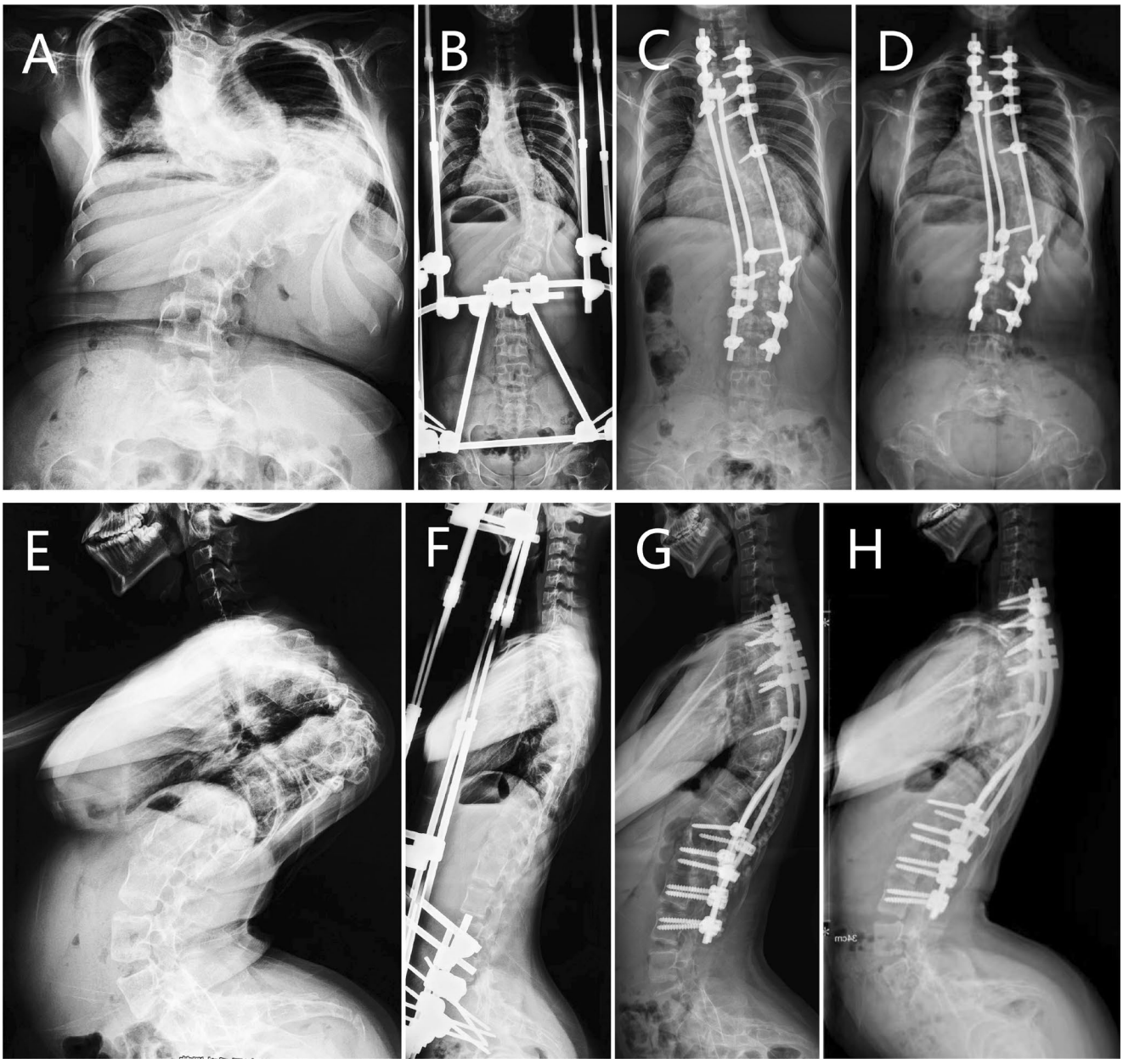

FIGURE 3 | Whole spine x-rays of Patient 4. (A, E) X-rays at the initial visit showing a thoracic curve of 89°, a thoracolumbar curve of 95°, and a T5 to T12 thoracic curve of 101°. (B, F) X-rays after the halo-pelvic device was applied. (C, G) Immediate postoperative x-rays after the correction surgery, following a 3-month traction. (D, H) X-rays at the latest follow-up.

thoracolumbar curve was reduced to 67°, and the kyphotic curve from T5 to T12 was reduced to 43° (Figure 3B,F, Table 1). Then, she received a kyphoscoliosis correction with posterior spinal fusion from T1 to L3. Immediately after surgery, the thoracic curve was corrected to 62°, the thoracolumbar curve was corrected to 58°, and the kyphotic curve from T5 to T12 was corrected to 9° (Figure 3C,G, Table S2). The 6-month postoperative follow-up outcomes were satisfactory (Figure 3D,H).

3.6 | Literature Review

A total of 86 articles were identified, of which 22 articles met the inclusion criteria. One article was excluded because the full-text content was not available. Among the included 21 articles, 73 patients with molecular confirmation were reported, with 17 of them from the same ancestors (Table S3). (Kypho)scoliosis was reported in 63 individuals. In the remaining 10 individuals, spinal features were missed in eight cases, one patient was reported to have spinal stenosis but without a recorded spinal curve, and another patient was evaluated shortly after birth with no detected spinal deformities.

(Kypho)scoliosis management was reported in 12 of the 63 patients and is summarized in Table 2. Spinal orthoses were prescribed for five patients, and surgeries were performed on nine patients. Among them, two patients received surgery after the use of orthoses. One patient received growing rod implantation after Halo-Gravity traction and followed by extensions; no complication was reported, but the detailed surgical plan was unknown [19, 35]. An unspecified growing device was applied to one patient, and a spinal fusion surgery was performed around 8 years

TABLE 2 | Literature review of (Kypho)scoliosis management in patients with *B3GALT6*-related disorders.

Patient No.	Age, gender	Reported management	References
2	20 years old, M	Surgery at 20 years old.	Coetzer et al. [34]
11	12 years and 7 months, M	Orthopedic corset from 4 years old. Surgery after Halo Gravity Traction. Three surgeries for lengthening until 10 years old.	Caraffi et al. [19] Nakajima et al. [35]
12	12 years and 11 months, M	Orthopedic corset from 2 years old.	Caraffi et al. [19]
20	4.5 years old, F	Bracing from 4.5 years old.	Van Damme et al. [8]
22	37 years old, M	Surgery at 15 years old, details unavailable.	Van Damme et al. [8]
28	15 years old, F	Spinal instrumentation with a growing device at 4.6 years and a final fusion at 12 years old.	Trejo et al. [20]
29	Died at 4 years old, F	Bracing, details unavailable.	Honey [36].
40	13 years old, M	Three fusion operations at 3, 4, and 11 years of age.	Vorster et al. [21] Beighton and Kozlowski [22]
41 (sibling of Patient 40)	10 years old, F	A fusion operation at 6 years old. A second operation was performed at 8 years old due to post-operative spinal instability.	Vorster et al. [21] Beighton and Kozlowski [22]
43	Died at 8 years old, M	Fusion operations, details unavailable. Died after a further operation at 8 years old.	Vorster et al. [21] Beighton and Kozlowski [22]
51	13 years old, F	Bracing from 5 years old, followed by 9 operations for spinal stabilization since 7 years old.	Vorster et al. [21] Beighton et al. [37]
70	34 years old, M	Surgery (inferred from X-ray), details unavailable.	Nakajima et al. [35]

later [20]. Studies also documented four patients who received repeated surgeries [22, 37]. Among them, spinal fusion surgeries were reported in three patients, with one requiring nine procedures. Spinal instability was reported to be the reason for repeated surgical procedures in two patients, and death from subsequent operation was reported in one patient [22, 37]. Surgeries have also been reported in another three patients, but further information, including the type of surgery, was not available.

4 | Discussion

In this study, we report surgical details and outcomes in patients with genetically confirmed *B3GALT6*-related disorders. Our findings suggest that selecting the STV as the LIV may enhance surgical outcomes, and Halo-pelvic traction is safe and effective. Furthermore, preoperative genetic testing plays an important role in surgical planning.

4.1 | Surgical Experience and Literature Review

4.1.1 | Selecting the STV as the LIV

The growing rod technique is widely used in treating early-onset scoliosis to control deformities while preserving growth. Complications, including wound healing and implantation failure, are commonly observed and are associated with additional procedures after the index surgery [38]. Although spinal surgeries in patients with *B3GALT6*-related disorders have been reported, details are not available. Most reports raise concerns regarding complications or potential complications associated with joint hypermobility, skin fragility, or vascular and organ fragility. No guidelines or specific recommendations have been developed. Limited evidence has been documented in patients with other types of EDS, and molecular diagnosis is not always available. Growing rod treatments with subsequent lengthening procedures, posterior spinal fusion, and Halo-Gravity traction have been reported in patients clinically or molecularly diagnosed with kyphoscoliotic EDS, arthrochalasia EDS, hypermobile EDS, musculocontractural EDS, and uncertain subtype. Complications are common, including infection, proximal junctional kyphosis, hook dislodgement, dysesthesia, blood loss and hemoperitoneum, and death has also been reported [39–41]. In patients with *B3GALT6*-related disorders, our literature review identified two growing rod implanting procedures and one of them was carried out following Halo-Gravity traction. However, the surgical details, including instrumentation levels, are not available. Spinal instability has been reported as a concern and resulted in repeated spinal fusions in multiple patients [22, 37]. Death from spinal surgery has also been reported [22]. Besides, surgery was considered but not performed in one patient due to the concern of instrumentation failure [42].

The distal adding-on phenomenon is one of the possible postoperative complications referring to the loss of correction. Selection of

the LIV is crucial in the prevention of the adding-on phenomenon as well as in the preservation of lumbar spinal mobility. However, its determination remains variable, and the optimal choice is still debated. Factors considered in the selection of the LIV typically include the type and severity of the curve, the flexibility of the spine, the location of the end vertebra, and the stable vertebra, as well as the patient's age and growth potential [43]. Some studies suggest that choosing a touched vertebra as the LIV is safe and at the same time saves more motion segments in patients with adolescent idiopathic scoliosis [44, 45]. However, a higher rate of adding-on has been reported when a nonsubstantially touched vertebra is selected as the LIV [46]. In the present study, Patient 1 received an index surgery for "early-onset scoliosis" without a molecular diagnosis. The selection of the instrumented segment was conventional to save levels, but a postoperative adding-on phenomenon was observed. Proximal junctional kyphosis (PJK) has been repeatedly reported in patients with EDS and may be caused by the hypermobility of the spine [40, 47]. Similarly, it was hypothesized that the L3-L4 facet dislocation resulting in the distal adding-on was caused by the pronounced joint hypermobility involving the spine. Therefore, the LIV was extended to the STV during the revision surgery, and the outcome was satisfactory. The LIV was similarly extended to the STV in subsequent patients with *B3GALT6*-related disorders, and no complication has been observed. Joint hypermobility usually directs attention toward the prevention of joint injuries. However, it should also remind spinal surgeons of the hypermobile spine, optimizing preoperative surgical decision-making.

4.1.2 | Feasibility of Halo-Pelvic Traction

Preoperative Halo traction is effective in treating severe scoliosis as it achieves gradual correction and improves pulmonary function. The specific plan is determined by factors such as the rigidity of the spine and the Cobb angle of the curve. The (kypho)scoliosis in Patient 4 was severe at the initial visit, but responded well to the Halo traction. It was possibly attributed to the hypermobility of the spine.

4.2 | Molecular Diagnosis-Informed Clinical Decision Making

4.2.1 | Surgical Planning Guided by Preoperative Molecular Diagnosis

Our experience also emphasizes the importance of preoperative molecular diagnosis, which enables personalized treatments and may help avoid complications. It is well recognized that the treatment of early-onset scoliosis is challenging due to the etiological heterogeneity. Studies show a higher occurrence of severe complications in patients with syndromic scoliosis as compared to those with idiopathic scoliosis [3]. In our previous study, 20% of the patients with EOS had underlying genetic disorders that may substantially impact the treatment strategy and allow for more well-informed decisions [25]. For example, an early diagnosis of malignant hyperthermia enables the use of alternative anesthetic agents, ensuring the patient's safety. At a spine clinic, a comprehensive preoperative evaluation, including deep phenotyping, may identify patients with multisystemic disorders, in which scoliosis is the earliest presentation that draws attention. For instance, features including soft, hyperextensible, and fragile skin, hypermobile joints, and easy bruising are indicative of HCTDs and should prompt further investigation, including genetic testing. A personalized management strategy structured under a multidisciplinary team framework for patients with HCTDs is necessary. Considering the multisystemic involvement and clinical heterogeneity, the multidisciplinary team (MDT) is recommended to comprise experts from essential departments, for example, orthopedic surgeons, vascular surgeons, dermatologists, geneticists, and nurses. This approach maximizes treatment outcomes.

4.2.2 | Optimal Management Guided by Timely Molecular Diagnosis

Even though surgical treatment achieved satisfactory results in our study, it may not be the optimal treatment option for patients with *B3GALT6*-related disorders if an earlier diagnosis can be reached. Considering factors such as joint and spinal hypermobility as well as reduced bone density, which may lead to increased risks of postoperative complications, conservative management methods should be exhausted before proceeding with surgical interventions [32, 48]. Although the use of orthoses did not prevent surgeries in the present and reported studies, it might have postponed the index surgery, thereby reducing complications [49]. Besides orthoses, physical therapy is an effective conservative management method for treating patients with mild idiopathic scoliosis [50]. Further studies are needed to investigate the effectiveness of physical therapy in controlling the progression of spinal deformities in patients with HCTDs, including *B3GALT6*-related disorders. Additionally, recent studies have identified spinal deformities as common features in *b3galt6*$^{-/-}$ larvae. Stimulating intrinsic compensational mechanisms has been proposed as a potential therapeutic intervention since it promotes the production of PGs, holding promise for gene-targeted therapies [51].

Additional attention should be paid to the impact of growth hormone treatment on the worsening of (kypho)scoliosis. In Patient 3, the progression of spinal deformities was reported after each of the two courses of growth hormone therapy, necessitating the index and revision surgeries, respectively. Therefore, an MDT approach, at least involving orthopedists, endocrinologists, and pediatricians, is strongly recommended to monitor development, increase adult height, and reduce adverse effects. Short stature is commonly observed in patients with *B3GALT6*-related disorders, and growth hormone therapy may be prescribed despite the absence of evidence. The association between growth hormone therapy and the development and progression of (kypho)scoliosis remains controversial, and certain syndromes causing short stature may pose additional risks [52, 53].

4.3 | Limitations and Strengths

Limitations largely due to the rarity of *B3GALT6*-related disorders are acknowledged in our study. Only a small number of patients were included in this study. While the findings presented here offer valuable insights, a larger sample size with longer follow-up periods would likely enhance the robustness and generalizability of the results.

Nonetheless, we present, for the first time, comprehensive surgical strategies that integrate disease manifestations with molecular findings and surgical considerations. Our experience in utilizing molecular diagnosis to inform surgical planning contributes valuable insights to the limited literature in this field.

5 | Conclusion

Stopping the LIV at the STV is recommended in spinal surgeries for patients with *B3GALT6*-related disorders, considering the joint hypermobility associated with the condition. Preoperative Halo-pelvic traction may also be safe and effective. Furthermore, preoperative molecular diagnosis is essential for enabling precision medicine and minimizing potential complications. In addition, preoperative conservative interventions should be exhausted before considering surgical treatment, and growth hormone treatment is recommended to be carried out under MDT approaches.

Author Contributions

Aoran Maheshati: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review and editing. **Kexin Xu:** conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review and editing. **Ziquan Li:** formal analysis, validation, writing – review and editing. **Guozhuang Li:** formal analysis, validation, writing – review and editing. **Xiangjie Yin:** formal analysis, writing – review and editing. **Qing Li:** formal analysis, writing – review and editing. **Di Liu:** formal analysis, writing – review and editing. **Shengru Wang:** formal analysis, resources, supervision, writing – review and editing. **Zhihong Wu:** funding acquisition, writing – review and editing. **Guixing Qiu:** funding acquisition, writing – review and editing. **Baozhong Zhang:** formal analysis, resources, supervision, writing – review and editing. **Terry Jianguo Zhang:** formal analysis, funding acquisition, resources, supervision, writing – review and editing. **Yu Wang:** formal analysis, resources, supervision, writing – review and editing. **Nan Wu:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, resources, supervision, writing – review and editing.

Acknowledgments

We thank our patients and families for participating in this study. We thank our colleagues at PUMCH and Peking University First Hospital for their contribution to this study.

Ethics Statement

This study was approved by the Ethics Committee at Peking Union Medical College Hospital (I-22PJ976) and the Ethics Committee at Peking University First Hospital (2021-285). Written informed consent was obtained from each patient's legal guardian.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

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